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Ortho-selectivity in the nucleophilic aromatic substitution (S_NAr) reactions of 3-substituted, 2,6-dichloropyridines with alkali metal alkoxides

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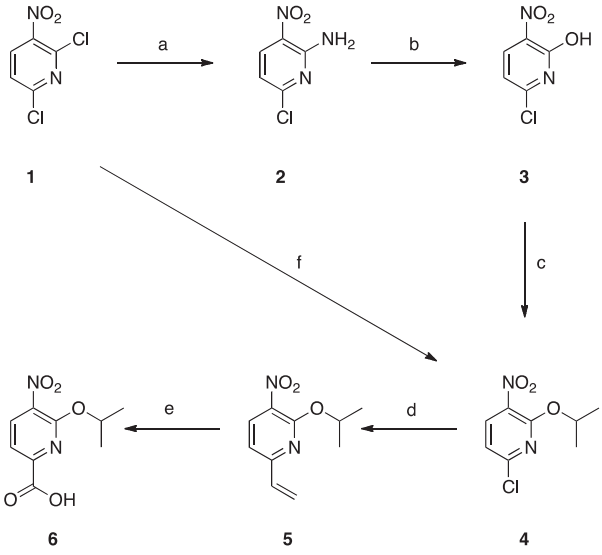
ABSTRACT

3-Substituted, 2,6-dichloropyridines have featured in the syntheses of small molecule inhibitors of a wide variety of biological targets. Hence, the regioselective displacement of the chlorines is of significant interest. Through conducting an extensive solvent study, we have found that non-polar, aprotic solvents of low hydrogen bond basicities favour substitution of the chlorine *ortho* to the 3-substituent by alkali metal alkoxides. We present convincing evidence that coordination of the alkali metal counter-ion to the 3-substituent (nitro, ester, amide) is the origin of the *ortho*-selectivity to give a cyclic, six-membered transition state. Excellent *ortho*-selectivities (⩾98:2) for secondary and tertiary alkoxides were realized with the sodium counter-ion, whereas the more reactive primary alkoxides required the harder, more Lewis acidic lithium counter-ion.

Coordination of Lewis basic groups to alkyllithiums has been exploited in the *ortho*-lithiation of arenes bearing a directing metalation group (DMG).[1] These intermediates can then be reacted with a variety of electrophiles in what is overall an adaptation of electrophilic aromatic substitution. Until very recently,[2,3] this directing effect had been somewhat overlooked in the nucleophilic aromatic substitution (S_NAr) reactions of 1-substituted, 2,4-dihaloaromatic compounds with metal alkoxides. In those publications,[2,3] however, there were no detailed discussions on the Lewis basicities of the reaction solvent and the electron-withdrawing/directing group (at the 1-position) and their relative abilities to promote *ortho* attack. In the more recent of the two papers, the scope of alkoxide nucleophile was not investigated. Furthermore, a comprehensive study of analogous reactions with the related 3-substituted, 2,6-dichloropyridines, in which metal cation coordination to the pyridine nitrogen could compromise the directing effect of the 3-substituent, has never been reported in the literature. This is surprising given their use in the development of a large number of small-molecule inhibitors of a variety of biological targets, as well in the synthesis of the pharmaceutical compound flupirtine.[4]

En route to the preparation of a new α-helix mimetic, compound **6** was required as a particular subunit. Previously, its synthesis has been accomplished via the lengthy fashion a through e in Scheme 1 in research that led to low micromolar antagonists of the Bak–Bcl-x_L complex.[5] This route is further hampered by the non-trivial regioselective alkylation of the pyridone oxygen,



Scheme 1. Reagents and conditions: (a) NH_3, EtOH; (b) $NaNO_2$, H_2SO_4, H_2O; (c) Ag_2CO_3, $(CH_3)_2CHI$; (d) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$; (e) (1) O_3, AcOH; (2) $AgNO_3$, KOH; (f) $(CH_3)_2CHOH$, NaH, toluene, 0 °C→rt, 16 h, 93%.

which requires the use of expensive silver carbonate.[6] We considered if compound **4** could be obtained from **1** in a single step by a regioselective S_NAr reaction. In this Letter, we reveal that non-polar solvents of low hydrogen bond basicities promote *ortho*-selective attack of 3-substituted, 2,6-dichloropyridines by alkali metal alk-

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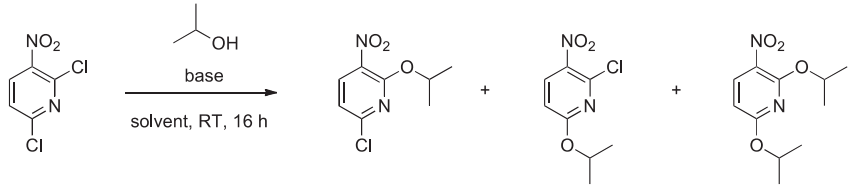
oxides through the formation of a cyclic, six-membered transition state containing the metal counter-ion, reminiscent of the *ortho*-lithiation of arenes. The effects of the solvent, metal counter-ion and directing group are explored, as is the scope of the alkoxide nucleophile.

Since the reaction of **1** with ammonia (and amines) to afford **2** is known to proceed with excellent *ortho*-selectivity,[7] we considered that this may be due to the formation of a stabilizing hydrogen bond in the transition state between the ammonia nucleophile and the nitro group of the electrophilic aryl chloride. Indeed, it has recently been shown that solvent hydrogen bond basicity (SHBB) has a dramatic effect on the regiochemistry of S_NAr reactions of electron deficient polyfluoroarenes with secondary amines through its effect on amine hydrogen bonding in the transition state.[8] 2,4-Difluoroacetophenone gives excellent *ortho*-selectivities in solvents of poor hydrogen bond basicities owing to the formation of a hydrogen-bonded, six-membered transition state that is not accessible upon *para* attack.[8] In turn, we speculated that *ortho*-selectivity with metal alkoxides might likewise be effected through coordination of the metal counter-ion with the nitro group to form an analogous six-membered transition state, and thus that we might be able to achieve the transformation of **1** into **4** in a single step. In addition to the obvious economical benefits, this would accelerate the development of small molecules incorporating this motif.

The conversion of substrate **1** into product **4** with in situ-generated sodium isopropoxide was initially conducted in DMF, a dipolar, aprotic solvent that is known to accelerate S_NAr reactions, and in the non-polar, aprotic solvent toluene. For the DMF reaction, all starting material was consumed within a matter of hours at room temperature to give an inseparable and approximate 2:1 mixture of **4a** and **4b**, as well as 8% of the bis-substituted by-product **4c**. Conversely, for the reaction in toluene, which required 16 h at room temperature for all starting material to be consumed, a ratio of **4a**:**4b** of 98:2 was achieved, with no detectable **4c**. Whilst it is anticipated that sodium isopropoxide is poorly soluble in toluene, it is envisaged that its solubility would be increased upon coordination of the sodium cation to the polar nitro group of **1**, bringing the associated nucleophilic isopropoxide anion into close proximity to the activated *ortho*-carbon. Thus, attack *ortho* to the nitro group would be favoured and would lead to an electrostatically neutral transition state, which would be favoured in solvents of low dielectric constant, such as toluene. This concept of 'built-in solvation' was first proposed by Bunnett for a similar system,[9] and would explain the *ortho* regiochemical outcome of this reaction. Confirmation of the *ortho*-selective attack of isopropoxide was acquired through ^{1}H and NOESY NMR analysis of **4a** and of a mixture of **4a**/**4b** (Supplementary data).

A variety of solvents was investigated to ascertain their effects on regioselectivities; the results of our findings are given in Table 1, and they are presented in order of decreasing *ortho*-selectivity. There is a correlation between the regiochemical outcome of the reaction and both the solvent's dielectric constant (ε_r) and its Taft pK_{HB} value.[10] The latter parameter can be used as a measurement of SHBB, which, given that hydrogen bonding is a special class of the Lewis acid-base interaction, presumably correlates well with Lewis basicity towards a given metal cation (Lewis acid). Solvents of lowest ε_r and pK_{HB} values furnished the highest regioselectivities. Conversely, solvents of highest ε_r and pK_{HB} values gave the lowest regioselectivities, and also led to greater amounts of bis-substituted product. Of the solvents studied, toluene afforded the best *ortho*-selectivity, whilst DMSO afforded the worst. It is noteworthy that for CH_3CN, DMF and DMSO, all of which have similar dielectric constants, a clear trend exists: the greater the pK_{HB}, the more reduced was the amount of *ortho* product. These results are consistent with our hypothesis that *ortho*-selectivity is achieved

Table 1
Solvent and counter-ion effects on the regioselectivity of the reaction[a]



1 **4a** **4b** **4c**

Entry	Solvent	ε_r[b]	pK_{HB}[c]	Base	Yield[d] (%)	Ratio **4a**:**4b**:**4c**[e]
1	Toluene	2.38	−0.363	NaH	93	98:2:0
2	Dioxane	2.21	1.033	NaH	82	93:6:1
3	CH_2Cl_2	8.93	−0.3[f]	NaH	90	92:7:1
4	THF	7.58	1.28	NaH	82	85:13:2
5	CH_3CN	35.94	0.913	NaH	50, 91[g]	72:26:2
6	Isopropanol	18.23	0.82	NaO^{i}Pr	57, 98[g]	67:33:0
7	DMF	36.71	2.103	NaH	70	59:33:8
8	DMSO	46.45	2.583	NaH	22	49:40:11
9[h]	Toluene	2.38	2.38	NaH	51, 97[g]	66:34:0
10	THF	7.58	1.28	LiHMDS	ND	94:6:0
11	THF	7.58	1.28	NaHMDS	ND	86:14:0
12	THF	7.58	1.28	KHMDS	ND	82:9:9

[a] Reaction conditions: 2,6-dichloro-3-nitropyridine (1 mmol) and isopropyl alcohol (1.2 mmol) were dissolved in the solvent (10 mL). The reaction was cooled to 0 °C (the DMSO reaction was performed at room temperature). NaH (1.3 mmol) was added under N_2. After 30 min, the reaction flask was removed from the ice bath and stirred for 16 h at rt.
[b] Relative dielectric constant.
[c] A scale for hydrogen bond basicity.
[d] Isolated yield after purification by silica gel flash column chromatography.
[e] Determined by ^{1}H NMR.
[f] Value for generic chloroalkane.
[g] Yield based on recovered starting material.
[h] Reaction performed with 1.2 mmol of 15-crown-5; NaH was added last. ND = not determined.

through coordination of the sodium cation to the nitro group, since the lower the solvent's polarity, the more poorly the sodium isopropoxide will be solvated and the lower the SSHB, the weaker will be its ability to coordinate (solvate) the sodium ions in particular. To acquire further proof that coordination of the sodium counter-ion is the 'key' to *ortho*-selectivity, we repeated the reaction in toluene but this time in the presence of 15-crown-5. Through comparing entries 1 and 9 in Table 1, it can be seen that the crown ether significantly reduced the regioselectivity of the S_NAr reaction, affording a similar result as that with dipolar, aprotic solvents like DMF (entry 7). Finally, we investigated the effect of the metal counter-ion on the regioselectivity of the reaction. Employing the lithium, sodium and potassium salts of hexamethyldisilazane (HMDS) as the base in THF, we observed that the identity of the metal counter-ion played a notable role (entries 10–12), with the amount of *ortho* product decreasing in the order $Li^+ > Na^+ > K^+$ (although the K^+ counter-ion led to a greater amount of bis-substituted product). This result makes sense, given that Li^+ is the hardest of all the alkali metal cations and can therefore form the strongest bonds with an oxygen of the nitro group. A plausible transition state for the *ortho* regiochemical outcome of this reaction is shown in Figure 1, and this is consistent with the data presented in Table 1.

The alkoxide substrate scope for this reaction was next explored. As can be seen in Table 2, primary, secondary and tertiary alkoxides all reacted in high yields and with excellent *ortho*/*para* regioselectivities of ⩾93:7. The hindered *tert*-butoxide anion demanded the use of an excess of the nucleophile as well as a reaction temperature of 60 °C; the yield and regioselectivity were not compromised by these more forcing conditions (entry 8). The highest regioselectivities were observed with the sodium salts of secondary and tertiary alkoxides. Given our findings in Table 1 on the effect of the metal counter-ion, we were able to boost the *ortho*-selective attack of primary alkoxides by invoking the lithium salt (compare entries 2 and 3). Thus, for complete formation of the *ortho* regioisomer, when the alkoxide is primary, the lithium salt should be used, whilst the sodium salt is suitable for secondary and tertiary alkoxides.

We next investigated the scope of this regioselective S_NAr reaction with 2,6-dichloropyridines carrying different substituents at the 3-position. To ensure the reaction still proceeded, electron-withdrawing groups were employed: nitrile, ester and amide, as well as nitro (data from Table 1). This time, sodium isopropoxide was added directly rather than being prepared in situ; notably, this led to more sluggish and incomplete reactions. Thus, we have presented both yields and yields based on recovered starting material. For each of the four 2,6-dichloropyridine substrates, the highest *ortho*-selectivity was obtained in toluene (Table 3), and the regioselectivity dropped as the solvent became progressively more polar and more able to solvate the sodium counter-ion (higher SHBB), consistent with the data in Table 1. When X was nitro, ester or amide, excellent *ortho*-selectivity (⩾97:3) was observed in all cases in toluene. However, a notable exception is 2,6-dichloronicotinonitrile, which gave a substantially reduced regioselectivity in toluene (entry 4) and no regioselectivity in CH_3CN (entry 6). These results were rather surprising at first, since we expected no regioselectivity would be observed in any solvent, given the digonal, *sp*-hybridized nature of

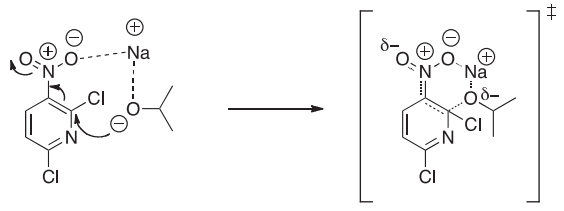
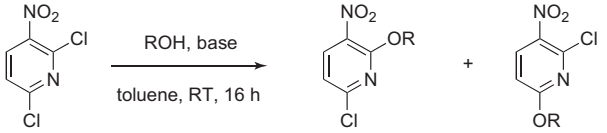
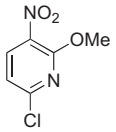
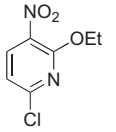
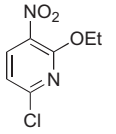
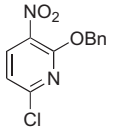
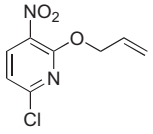
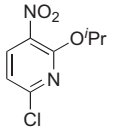
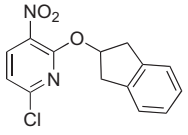
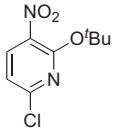


Figure 1. Built-in solvation of sodium isopropoxide by the nitro group accounts for the *ortho*-selectivity of the S_NAr reaction in non-polar solvents of poor hydrogen bond basicities (pK_{HB}), such as toluene.

Table 2
Substrate scope for the reaction of 2,6-dichloro-3-nitropyridine with a variety of alkali metal alkoxides[a]

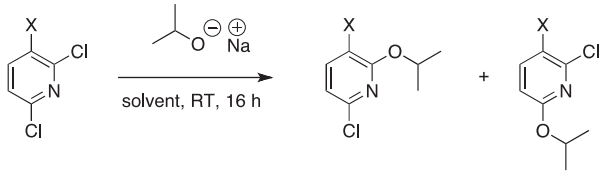


1 A B

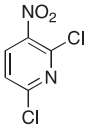
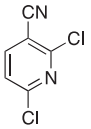
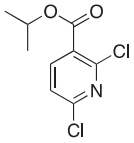
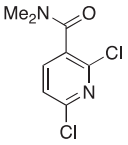
Entry	Product	Base	Yield[b] (%)	Ratio, A:B[c]
1[d,e]		NaH	81	93:7
2		NaH	76	94:6
3		LiHMDS[f]	91	99:1
4		NaH	68, 97[g]	93:7
5		NaH	94	96:4
6		NaH	93	98:2
7		NaH	84	99:1
8[h]		NaH	95	100:0

[a] Reaction conditions: 2,6-dichloro-3-nitropyridine (1 mmol) and the alcohol (1.2 mmol) were dissolved in toluene (10 mL). The reaction was cooled to 0 °C (the DMSO reaction was performed at room temperature). NaH (1.3 mmol) was added under N_2. After 30 min, the reaction flask was removed from the ice bath and stirred for 16 h at rt.
[b] Isolated yield after purification by silica gel flash column chromatography.
[c] Determined by ^1H NMR.
[d] To minimize bis-substitution, sodium methoxide was first generated in situ and then the pyridine was added.
[e] Approximately 7% of bis-substituted by-product was detected.
[f] 3 equiv of LiHMDS used.
[g] Yield based on recovered starting material.
[h] Modified reaction conditions: 2.6 equiv *tert*-butanol, 2.8 equiv NaH, 60 °C, 30 min.

Table 3
Substrate scope for the reaction of sodium isopropoxide with 3-substituted, 2,6-dichloropyridines[a]



1 A B

Entry	2,6-Dichloropyridine	Approximate pK_b of X[12]	Solvent	Yield[b] (%)	Ratio, A:B[c]
1[d]		26	Toluene	93	98:2
2[d]			Dioxane	82	94:6
3[d]			CH_3CN	50, 91[e]	74:26
4		24	Toluene	69, 93[e]	72:28
5			Dioxane	95	66:34
6			CH_3CN	92	53:47
7		21	Toluene	53, 83[e]	98:2
8			Dioxane	67, 82[e]	94:6
9			CH_3CN	78, 85[e]	79:21
10		15	Toluene	51, 92[e]	97:3
11			Dioxane	60, 92[e]	95:5
12			CH_3CN	71, 87[e]	88:12

[a] Reaction conditions: 2,6-dichloro-3-X-pyridine (0.5 mmol) was dissolved in the solvent (5 mL), then sodium isopropoxide (1.5 mmol) was added. The reaction was stirred at room temperature for 16 h.
[b] Isolated yield after purification by silica gel flash column chromatography.
[c] Determined by ^{1}H NMR.
[d] Data from Table 1 with sodium isopropoxide generated in situ.
[e] Yield based on recovered starting material.

the nitrile functionality which directs the N lone pair away from a favoured, six-membered transition state. Although less common, nitriles are known to engage in 'side-on' π-coordination with metals and metal cations in which the C–N triple bond acts as the Lewis base,[11] in contrast to 'end-on' σ-coordination through the nitrogen lone pair. Side-on coordination would afford a transition state more akin, but less optimal, to that presented in Figure 1, and would explain the less pronounced *ortho*-selectivity.

The stronger a base (lower pK_b), the more thermodynamically favourable is its reaction with an acid. Invoking the broader Lewis definition of acids and bases, it follows that more basic (electron pair-donating) functional groups will coordinate more strongly to a given metal cation (Lewis acid). Excepting the data for 2,6-dichloronicotinonitrile for the reason just described, there is a clear effect of the basicity (pK_b) of the X group, which correlates well with its Lewis basicity, on the regiochemical outcome of the reaction in CH_3CN (entries 3, 9 and 12). An increase in *ortho* product was observed in the order nitro < ester < amide, in line with the increasing basicities[12] of these groups.

In conclusion, we have demonstrated that S_NAr reactions of 3-substituted, 2,6-dichloropyridines with alkali metal alkoxides proceed with excellent *ortho*-selectivities (*ortho* with respect to the 3-substituent). A broad range of alkoxides was examined: complete, or almost complete (⩾98:2), *ortho*-selectivity with secondary and tertiary alkoxides was realized with the sodium counter-ion, whilst the more reactive primary alkoxides required the more Lewis acidic lithium counter-ion. Through conducting a solvent study, experiments with 15-crown-5 and performing the S_NAr reaction on 2,6-dichloropyridines with varying 3-substituents, we have provided evidence that coordination of the metal counter-ion to the 3-substituent is the origin of the regioselectivity. Given that 3-substituted, 2,6-dichloropyridines have featured in the design of a large number of small-molecule inhibitors, we feel the work reported herein may be of significant interest.

Acknowledgements

The authors wish to thank the University of Maryland School of Pharmacy and the American Association of Colleges of Pharmacy (AACP) for financial support of this work, and Dr. Andrew Coop for helpful discussions.

Supplementary data

Supplementary data (^{1}H NMR spectrum of **4a**, and ^{1}H and NOESY NMR spectra of a mixture of **4a**/**4b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.007.

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12. pK_b values determined from entering pK_a values (taken from http://evans.harvard.edu/pdf/evans_pKa_table.pdf) of the protonated X groups into the equation $pK_w = pK_a + pK_b$, where $pK_w = 14$.